N-Permethylation of Primary and Secondary Aromatic Amines

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N-Methylation of the amino function to give a tertiary amine is an important but sometimes problematic reaction. A large number of reagents may be used for this purpose; however, several serious drawbacks are encountered. Classical examples of shortcomings[1] of the established methylation procedures are, for example, the formation of complex mixtures of unalkylated, partially methylated, and quaternary products, or *C*-sulfonation when aromatic amines are methylated with dimethyl sulfate. Some of the methods proposed to overcome such drawbacks are the use of formaldehyde/sodium or potassium hydridotetracarbonylferrate in ethanol or tetrahydrofuran[2], of formaldehyde/sodium borohydride in methanol[3], and of formaldehyde/sodium cyanotrihydridoborate in acetonitrile[4]. The first of these methods may involve a rather tedious work-up, the second one may give rise to the formation of aminodiethers, and the third one produces cyanide ion. All three methods have been claimed to be useful alternatives for the Eschweiler-Clarke alkylation with formaldehyde/formic acid[5] which has only limited applicability in the case of aromatic amines because ring alkylation reactions may occur.

We have earlier reported a modification of the formaldehyde/borohydride method[6] by which the methylation is carried out in an aqueous-acidic (sulfuric acid) medium. Using this modified method, high conversions to tertiary methylated amines were obtained from aliphatic polyamines. We now report an extension of this method to the *N*-methylation of primary and secondary aromatic amines to give methylated tertiary amines. The order of mixing of the reagents had to be altered in order to avoid long contact times between the amines and formaldehyde in acidic solution[7]: A slurry of sodium borohydride in tetrahydrofuran containing the amine is added to a mixture of 3 molar sulfuric acid, 40% aqueous formaldehyde, and tetrahydrofuran. All reagents are used in stoichiometric excess over the amount of amine to be methylated.

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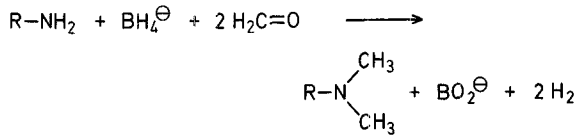
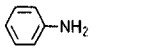
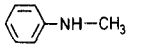
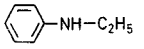
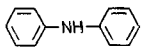
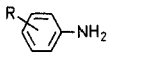
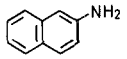
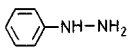
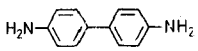
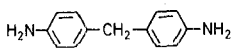
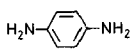


G.L.C. analysis showed 84–100% yields of methylated tertiary amines although the reaction conditions had not been optimized. The yields of isolated (distilled or recrystallized) products parallel the analytical yields. We also carried out the reaction on a larger scale (5 g of amine) and found that the yields are not affected by the scale of the reaction. The yields reported are average yields of 2–6 runs for each amine (Table 1).

We did not encounter any problems in the alkylation of low-basicity amines such as 4-nitroaniline (yield: 92–100%). Also, 2,6-dimethylaniline and 2,4,6-trimethylaniline which might exhibit steric hindrance to *N*-substitution were smoothly converted into the *N*,*N*-dimethyl derivatives whereas a previously reported[8] procedure for the preparation of *N*,*N*,2,4,6-pentamethylaniline from 2,4,6-trimethylaniline using formaldehyde and zinc amalgam in acetic-hydrochloric acid was cumbersone and afforded a 70% yield (our yield: 79%). Halogens on the aromatic ring as well as the N—N bond of phenylhydrazine are not affected by the reducing agent whereas the hydrazine moiety is trimethylated.

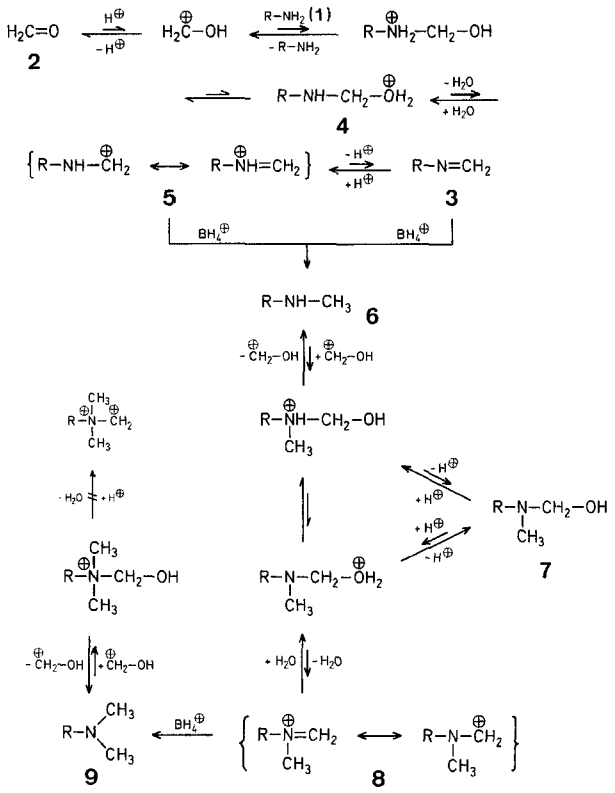
Replacement of tetrahydrofuran by 95% ethanol affords high yields with a number of amines (Table 2) and the formation of amino ethers or other side products is not observed. However, the yields are somewhat reduced in the case of sterically hindered anilines. The use of ethanol as solvent offers the advantage of a homogeneous and therefore better controllable reaction.

Table 1. *N*-Methylation of Primary and Secondary Aromatic Amines with Formaldehyde/Sodium Borohydride in Aqueous Tetrahydrofuran

Substrate	Number of methyl groups introduced	Small-scale procedure (50–400 mg) Yield [%] (by G.L.C. analysis)	Medium-scale procedure (5 g) Yield [%] by G.L.C. analysis	Yield [%] of isolated Product	m.p. or b.p./torr [°C] found	reported
	2	98	98	77	b.p. 78–81°/15 torr	b.p. 77°/13[9]
	1	98				
	1	87				
	1	93				
						
R = 2-CH_3	2	98				
3-CH_3	2	98				
4-CH_3	2	94				
2,3-di-CH_3	2	100				
2,4-di-CH_3	2	99				
2,5-di-CH_3	2	96				
2,6-di-CH_3	2	99				
3,4-di-CH_3	2	98				
3,5-di-CH_3	2	97	82	63 (crude)	b.p. 101–103°/18	b.p. 228.5–229°/760
2,4,6-tri-CH_3	2	95	96	79	b.p. 97°/18	b.p. 93.5–94°/12[9]
2-OCH_3	2	93				
3-OCH_3	2	98				
4-OCH_3	2	96	96	66	b.p. 105°/1 m.p. 45–47°	m.p. 48°[9]
4-F	2	99				
4-Cl	2	98				
4-Br	2	95				
3-NO_2	2	100				
4-NO_2	2	93	100	80	m.p. 160–162°	m.p. 161–162°[9]
	2	87				
	2	95				
	3	96				
	4	98				
	4	86				
	4	100				

The tertiary amines obtained in the preparative-scale runs are free from secondary amines (monomethylation products) and other contamination according to G.L.C. analysis (limit of detectability: $<0.1\%$).

The *N*-methylation of primary amines may be assumed to proceed by the following mechanism:



The first step consists of the formation of the imine **3** from formaldehyde **(2)** and the primary amine **1** in an acidic medium via the protonated *N*-hydroxymethylamine **4**. The imine **3** or its protonated form **5** is reduced to the *N*-methylamine **6** by sodium borohydride. In a similar sequence, the secondary amine **6** is then *N*-hydroxymethylated to give the unstable *N*-hydroxymethylamine **7** which, under the acidic conditions, is converted to the iminium cation **8**; reduction of **8** then affords the tertiary amine **9**. Side reactions such as the reduction of formaldehyde **(2)** or proton transfer from protonated species to borohydride ion proceed only to a minor extent, possibly due to the strong carbenium-ion reactivity of the iminium species **5** and **8**.

The proposed mechanism implies that the cation species **8** is more readily reduced than the cation species **5**. On the other hand, the extremely low concentration of **8** (due to unfavorable equilibria) seems to slow down the immediate methylation of the secondary amine **6** as soon as it is formed. This assumption is supported by the results obtained from the reaction of aniline using different amounts of sodium borohydride; below a certain ratio reducing agent/amine, *N*-methylaniline is formed in significant amounts (Table 3).

The presence of acid in the reaction medium is essential; at pH 6, the sequence does not proceed.

The method described here has the advantage that permethylation to the quaternary ammonium salts does not occur.

All starting materials used were commercially available (purity: >97%); however, the yields were calculated as if the starting materials were 100% pure. G.L.C. analyses were carried out under the following conditions: steel columns (A: 1 m, 2 mm ∅, Carbowax 20 M 5% – KOH 5 % on Chromosorb W 80–100 mesh; B: 2 m, 2 mm ∅, Carbowax 20 M 10% on Chromosorb W 80–100 mesh; C: 2 m, 2 mm ∅, Silicone SE 52 5% on Chromosorb W 80–100 mesh); flame-ionization detector; internal standards were used to determine G.L.C. yields in the reaction mixtures (weight/area correlation).

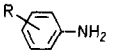
All reactions were performed at least three times under the conditions given in the experimental procedures; the results reported in Tables 1 and 2 are average values of these runs. The amount of amine used were 50–400 mg for the small-scale procedures; scaling up to 1–2 g simplified performance (temperature control, stirring).

The product tertiary amines were analyzed by mass-, I.R.-, and ^{1}H-N.M.R. spectrometry. The structures of all products were confirmed by comparison with authentic samples or by comparison of the physical data found with the corresponding literature data. All melting points are uncorrected.

N-Methylation of Primary and Secondary Aromatic Amines; Small-Scale Procedure:

A slurry of the aromatic amine (primary monoamines: 1 mmol; secondary amines: 2.0 mmol; diamines: 0.5 mmol; phenylhydrazine: 0.75 mmol) and finely crushed sodium borohydride (272 mg, 7 mmol) in tetrahydrofuran (7 ml) is added to a stirred mixture of 3 molar sulfuric acid (0.81 ml, 0.25 mmol) and 40% aqueous formaldehyde (0.46 ml, 6 mmol) in an Erlenmeyer flask at a rate compatible with temperature control ($-10°$ to $+20°$C). After the addition is complete, the mixture is made strongly basic with solid sodium hydroxide. The supernatant solution is decanted (and saved), the residue is treated with water (10 ml), and the resultant mixture is extracted with ether (2×20 ml). The organic solutions are combined, washed with saturated sodium chloride solution (10 ml), and dried with sodium sulfate. The solution is then analyzed by G.L.C. and/or the product isolated by preparative G.L.C. or by laboratory methods such as sublimation, microdistillation, or thick-layer chromatography.

Table 2. *N,N*-Dimethylation of Anilines with Formaldehyde/Sodium Borohydride in Aqueous Ethanol[a]

Substrate	Yield [%] of G.L.C. analysis	(Yield [%] obtained in Tetrahydrofuran)
		
R = H	98	(98)
2-CH_3	85	(98)
3-CH_3	98	(94)
4-CH_3	94	(100)
2,4-di-CH_3	47	(96)
2,3-*di*-CH_3	82	(99)
2,6-di-CH_3	54	(98)
2,4,6-tri-CH_3	15	(93)
2-OCH_3	83	(98)

[a] Results obtained using the small-scale procedure.

Table 3. Effect of the Ratio Amine/Sodium Borohydride in the Methylation of Aniline with Formaldehyde/Sodium Borohydride[a]

Aniline/$NaBH_4$ (mol/mol)	Yield [%] by G.L.C. analysis	
	N,N-Dimethylaniline	*N*-Methylaniline
0.50	100	0
1.31	71	12
2.35	24	26

[a] The reactions were carried out according to the small-scale procedure using 0.5 mmol of aniline, 1.5 mmol of 3 molar sulfuric acid, and 3.3 mmol of formaldehyde (35% by weight in water).

In order to ensure efficient stirring of the initial aqueous mixture, tetrahydrofuran (5 ml) may be added. The amount of acid used at the beginning may be reduced to about one half and the remaining acid be added portionwise as soon as the pH value exceeds 3.0.

In the above procedure, tetrahydrofuran may in part or completely be replaced by ethanol. Ethanol solubilizes sodium borohydride but it should be distilled off from the acidic solution before the final extraction with ether.

With amines of low ring nucleophilicity (such as nitroanilines), the usual addition procedure[6] may be followed.

N-Methylation of Aniline; Medium-Scale Procedure:
A slurry of aniline (2.524 g, 27.1 mmol) and finely crushed sodium borohydride (5.981 g, 158 mmol) in tetrahydrofuran (50 ml) is added dropwise to an efficiently stirred solution of 3 molar sulfuric acid (7 ml, 21 mmol) and 35% aqueous formaldehyde (8.3 ml, 110 mmol) in tetrahydrofuran (50 ml) at 10–30 °C. After the first half of the addition, the mixture is acidified with 3 molar sulfuric acid (7 ml, 21 mmol) and the addition then continued. To the resultant mixture, water (50 ml) is added with stirring, followed by the addition of solid potassium hydroxide to strongly basic reaction. The organic phase is separated and the aqueous phase extracted with ether (2 × 50 ml). The organic phases are combined (some water separates), washed with saturated sodium chloride solution (20 ml), and dried with sodium sulfate. The ether is evaporated and the residual N,N-*dimethylaniline* distilled in vacuo; yield: 2.52 g (77%); b.p. 78–81 °C/15 torr (Ref.[9], b.p. 77 °C/13 torr).

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